Clinical Value of Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography in Differentiation of Malignant Mesothelioma from Asbestos-Related Benign Pleural Disease

An Observational Pilot Study

Huseyin Yildirim, MD, Muzaffer Metintas, MD,* Emre Entok, MD,† Guntulu Ak, MD,* Ilknur Ak, MD,† Emine Dundar, MD,‡ and Sinan Erginel, MD**

Background: Several studies have already addressed the potential role of an increased fluorine 18 fluorodeoxyglucose (^{18}F FDG) uptake in identification of pleural malignancy. In this pilot study, we investigate the role of ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) for differentiating asbestos-related benign pleural disease from malignant mesothelioma.

Materials and Methods: The study population comprised 31 consecutive patients (17 malignant mesotheliomas, nine benign asbestos pleurisies, and five diffuse pleural fibrosis) with a mean age of 61 years between January 2006 and December 2008. Thoracoscopy or image-guided pleural needle biopsy were systematically performed to reveal pathologic diagnosis and/or clinical follow-up for at least 3 years for presence or absence of malignant pleural effusion. ROCs analyses for standardized uptake value (SUV) adjusted to body weight were calculated between benign and malignant pleural diseases.

Results: ^{18}F-FDG PET/CT imaging correctly detected the presence of malignancies in 15 of 17 patients with malignant mesothelioma for sensitivity, specificity, and overall accuracy of 88.2%, 92.9%, and 90.3%, respectively. ^{18}F-FDG PET/CT imaging correctly identified 13 of 14 cases of benign pleural disease. The mean SUV values were 6.5 ± 3.4 for malignant mesothelioma cases and 0.8 ± 0.6 for benign pleural diseases ($p < 0.001$). When we compared the two groups of pleural disease, a cut-off value of 2.2 for SUV gave the best accuracy with 94.1%, 100%, 100%, and 93.3% for sensitivity, specificity, positive predictive value, and negative predictive value, respectively.

Conclusion: Preliminary results of this trial provide evidence that ^{18}F-FDG PET/CT imaging is a highly accurate and reliable noninvasive test to decide for further investigation of differentiating malignant mesothelioma from benign pleural disease.

Key Words: ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography, Asbestos, Pleural disease, Malignant mesothelioma, Diffuse pleural thickening, Benign asbestos-related pleural effusions.

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Asbestos-related lung diseases have emerged as a major worldwide public health problem. Asbestos is a mineral that has been extensively mined and used for a large number of purposes all over the world. Exposure to asbestos, either occupational or environmental, is strongly correlated with the development of malignant pleural mesothelioma (MPM). Apart from malignant diseases, it is also well known that asbestos can cause benign lesions of the pleura, including pleural plaques, benign asbestos-related pleural effusion (BAPE), and diffuse pleural thickening (DPT).[1] The median survival after the diagnosis of pleural mesothelioma is between 9 and 12 months.[2] The management of patients with MPM is controversial. Multimodality regimens combining chemotherapy, radiotherapy, immunotherapy, and surgery are being used more frequently in patient management.[3] It is well known that the best chance for long-term survival is achieved with early diagnosis and aggressive surgery. For this reason, early discrimination between MPM and benign pleural disease is important for treatment and prognosis.[4]

Imaging plays a pivotal role in the diagnosis and subsequent management of patients with pleural disease. A plain chest radiography is usually the first imaging for mesothelioma. Today, computed tomography (CT) and magnetic resonance imaging have been widely used as the primary imaging modality for the diagnosis, staging, and monitoring of therapeutic response in mesothelioma.[5] The positron emission tomography (PET)/CT system has become widespread and plays an important role in clinical oncology. The clinical

Departments of *Chest Diseases, †Nuclear Medicine, and ‡Pathology, Medical Faculty, Osmangazi University, Eskisehir, Turkey.

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Address for correspondence: Huseyin Yildirim, MD, Department of Chest Disease, Medical Faculty, Osmangazi University, 26480 Meselik, Eskisehir, Turkey. E-mail: heylul2002@yahoo.com

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utility of fluorine 18 fluorodeoxyglucose (^{18}F-FDG) PET/CT in evaluating pleural malignancies has not been well defined.

Although these imaging techniques can be valuable in assessing the possibility of the MPM, certain diagnosis is still most often established through pleural fluid examination or tissue biopsy. However, cytologic examination of pleural fluid and closed pleural biopsy is relatively insensitive to reach the diagnosis. In a previous study from our group, we have shown that the diagnosis of MPM was made with CT-guided pleural needle biopsy in 83.3% of cases.[6] On the other hand, tissue samples can be obtained through thoracoscopy with a diagnostic sensitivity of more than 90%, but it is an invasive procedure and cannot be used for patients with progressive disease or advanced in age.

The aim of this study was to report our clinical experience with ^{18}F-FDG PET/CT for differentiating between MPM and asbestos-related benign pleural disease.

PATIENTS AND METHODS

Patients

An observational pilot study was performed in patients with pleural disease consecutively admitted to our hospital from January 2006 to December 2008. The study population consisted of 31 patients with pleural effusions or pleural thickening who were recruited from the Department of Chest Disease, Eskisehir Osmangazi University, Turkey. According to their final diagnosis, the patients were subdivided into three groups: patients with MPM ($n = 17$), patients with DPT ($n = 5$), and patients with BAPE ($n = 9$). A benign group was identified through a chart review of patients who had been followed at our hospital, and these patients were invited to perform FDG-PET study. The patients with DPT or BAPE were followed in 6 months intervals for the first 3 years and then annually by CT. Physical examination, chest radiography, and ^{18}F-FDG PET/CT scans were obtained in all patients who gave informed consent. Exclusion criteria were any concomitant infectious disease, previous therapy against MPM, or patients with metastatic pleural disease.

To be included into the analyzed group, patients were classified into different diagnostic groups based on the following explicit criteria:

1. DPT defined on the basis of chest radiograph or CT scan results. On a plain chest radiography, DPT is characterized by bilateral thickening involving at least 25% of the chest or 50% if unilateral, pleural thickening greater than 5 mm at any site, and obliteration of the costophrenic angle. On CT, DPT is defined as continuous sheet of thickening at least 5 cm in lateral extent 8 to 10 cm in craniocaudal extent and with a 3-mm thickness.[5] All patients with DPT had been followed for 3 years.
2. BAPE: Diagnostic criteria of BAPE include history of direct or indirect exposure to asbestos, exclusion of other causes of effusion by thoracoscopy or diagnostic thoracotomy, particularly tuberculosis and malignancy, and no malignancy detected within 3 years after the onset of the effusion.[7]
3. MPM cases were diagnosed histopathologically.

FDG-PET Imaging

^{18}F-FDG PET/CT imaging was performed at baseline within the 2 weeks before invasive procedure. All patients fasted for at least 6 hours before PET/CT examination, and their blood glucose concentrations were measured by finger stick. The injected dose of ^{18}F-FDG (Monrol, Kocaeli, Turkey) varied between 350 and 450 MBq depending on the patient's weight. Image acquisition was performed using an integrated PET/CT device (Biograph 6 Hirez PET/CT, Siemens, Knoxville, TN). CT was performed from the head to the pelvic floor using a standardized protocol (120 KV, 80 mA with a slice thickness of 5 mm). PET images were acquired using 3D mode for the same scanning range as CT. The acquisition time for PET was 3 minutes per bed position, and 5 to 6 continuous positions were scanned. PET images datasets were reconstructed iteratively using an ordered subset expectation maximization algorithm and corrected with measured attenuation correction. The images were assessed visually on axial, coronary, and sagittal reconstruction. All areas with abnormally increased ^{18}F-FDG uptake corresponding to a CT abnormality were interpreted as positive for malignancies. Suggestive findings on CT were interpreted as negative if they did not correspond to an area of abnormally increased ^{18}F-FDG uptake. For a semiquantitative analysis of metabolic activity, a regions of interest (ROIs) analysis was performed. The ROIs were drawn manually around areas of the lesions. The ROIs data were used to calculate standardized uptake values (SUVs) on the ^{18}F-FDG PET/CT images. The SUV was determined according to the standard formula, with activity in the ROIs given in Bq/ml per injected dose in Bq/weight.

Outcomes were assessed by nuclear physician who were aware of patients histopathological diagnosis and clinical status.

Histopathology

Each of the biopsy specimens obtained by invasive procedures such as CT-guided pleural biopsy, thoracoscopy, or diagnostic thoracotomy were reviewed by trained single pathologists in our institute, and all mesothelioma cases were diagnosed using the currently accepted histologic criteria combined with the immunohistochemical features. A panel of antibodies (cytokeratin cocktail, calretinin, epithelial membrane antigen, carcinoembryonic antigen and Ber EP4, and WT1) was applied for distinguishing mesothelioma from metastatic carcinoma.

Statistical Analysis

All statistical tests were performed out using SPSS (version 10.0; SPSS Inc., Chicago, IL). The χ^2 test was used to evaluate the association between categorized variables. The Mann-Whitney U test was used to compare SUVmax of malignant mesothelioma with those of benign pleural disease. A receiver operating characteristic (ROC) curve were generated using commercial software, and the optimal cut-off point was determined for SUVmax. All tests were considered significant at $p < 0.05$.

RESULTS

A total of 40 patients were enrolled in the study. Nine patients were excluded from the analysis because of metastatic pleural disease ($n = 5$), tuberculous pleural effusions ($n = 3$), and incomplete follow-up ($n = 1$). The patient cohort consisted of 31 patients (20 men and 11 women), with a mean age of 61 years (range, 40–82 years). MPM was diagnosed in 17 patients, DPT in five patients, and BAPE in nine patients. From the 17 patients with MPM, 11 (64.7%) were of epithelioid mesothelioma, three (17.6%) were biphasic mesotheliomas, two (11.8%) were sarcomatoid mesothelioma, and one (5.9%) was undetermined subtype. There was a significant difference in the mean exposure duration between malignant and benign groups (30.9 years versus 12.3 years, respectively; $p < 0.05$).

In the malignant group, six patients were diagnosed by open pleural biopsy at thoracotomy, and 11 patients were diagnosed by a transpleural method: closed pleural needle biopsy ($n = 5$), medical thoracoscopy ($n = 3$), and transthoracic needle biopsy ($n = 3$). By contrast, in the benign group, diagnosis were obtained by closed pleural needle biopsy in three patients, medical thoracoscopy in four patients, and open pleural biopsy at thoracotomy in one patient. Of this latter group, the remaining six patients underwent at least 3 years of clinical follow-up documenting no clinical or radiologic progression of their disease.

Overall, ^{18}F-FDG PET/CT imaging correctly detected 15 of 17 cases of MPM by the reports of the Department of Nuclear Medicine (Figure 1). Two patients were not correctly identified by metabolic imaging with an absence of FDG uptake. One patient had a histologically confirmed epithelial subtype, and one had a sarcomatoid subtype. ^{18}F-FDG PET/CT imaging correctly detected 13 of 14 benign lesions. Furthermore, ^{18}F-FDG PET/CT scan results were falsely interpreted as positive in a patient with histologic diagnosis of DPT. In all patients with BAPE, ^{18}F-FDG PET/CT imaging revealed an absence of FDG uptake within the pleura. A patient with a false-positive PET result was still alive at a median follow-up

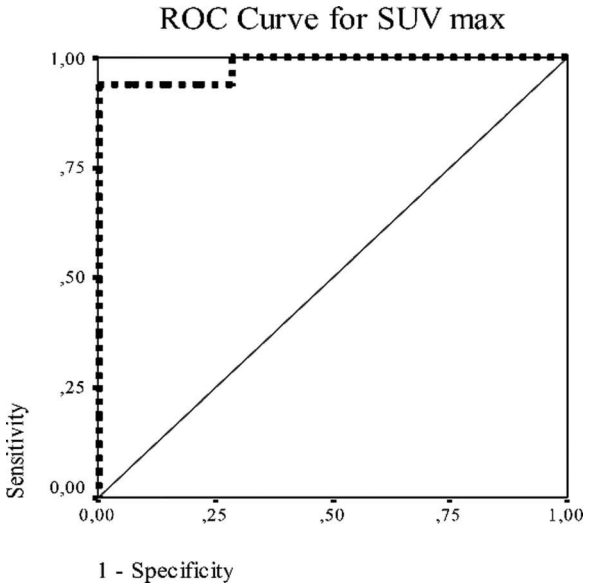

FIGURE 2. Receiver operating characteristic (ROC) curve for standardized uptake value (SUV). The area under the ROC curve for SUVmax was 0.983.

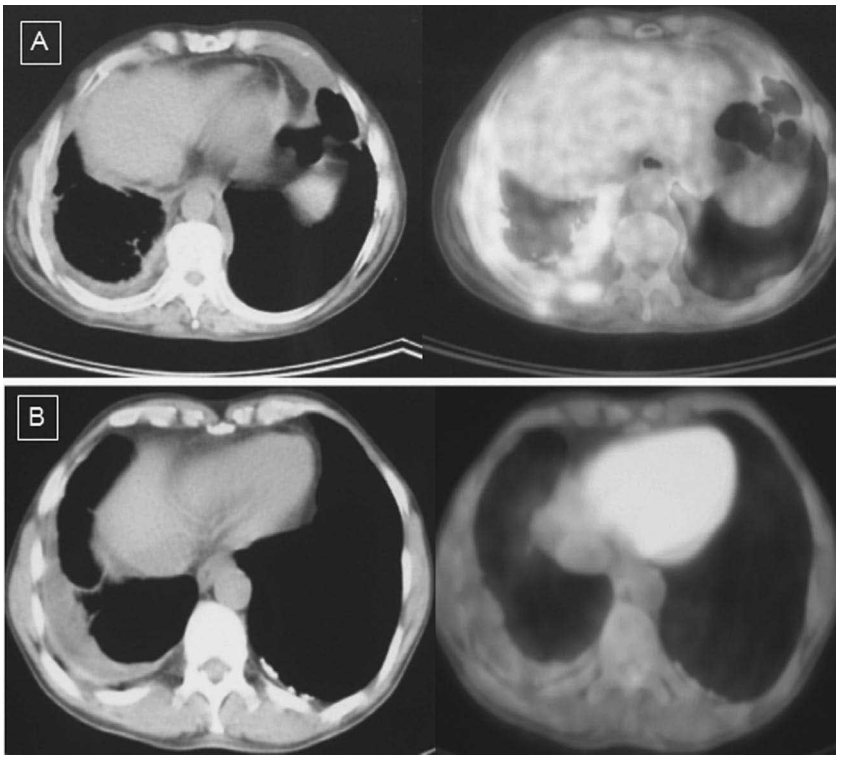

FIGURE 1. In patients with malignant mesothelioma, transverse FDG imaging revealed extensive pleural involvement of the right pleura with a maximal standardized uptake value of 6.25 (*A*, top). In a case of a benign pleural lesion, PET imaging revealed an absence of FDG uptake within the pleura, and this image suggests the benign nature of this lesion (*B*, bottom).

25 months with no signs or symptoms of malignancies. For the above results, the sensitivity of ^{18}F-FDG PET/CT imaging to detect pleural mesothelioma was 88.2%, the specificity was 92.9%, and overall accuracy was 90.3%.

The uptake of FDG was significantly higher in patients with mesothelioma than in benign lesions. The mean SUVmax in MPM was 6.5 ± 3.4, whereas the mean SUVmax in benign pleural disease was 0.8 ± 0.6, and the differences were statistically significant ($p < 0.001$). In the ROC analysis, we calculated SUV of more than 2.2 for SUV as having the highest diagnostic accuracy (Figure 2). In one patient who was diagnosed malignant mesothelioma, the obtained SUVmax value was below the calculated cut-off level (SUVmax = 1.49). We calculated that the sensitivity, specificity, positive predictive value, and negative predictive value of this value were 94.1%, 100%, 100%, and 93.3%, respectively.

DISCUSSION

The differentiation between malignant mesothelioma and asbestosis-related benign pleural disease poses a diagnostic challenge to the physician. Our study suggests that ^{18}F-FDG PET/CT is an effective tool that differentiates malignant from benign pleural disease with sensitivity of 88.2% and specificity of 92.9% according to the expert reports from the Department of Nuclear Medicine. Thus, ^{18}F-FDG PET/CT was useful for the characterization of asbestosis-related benign pleural disease, helping avoid unnecessary invasive procedures.

We found that ^{18}F-FDG PET/CT facilitated the detection of the tumor in 88.2% of cases. In 15 of 17 patients, there was FDG avidity representing MPM. In two of our malignant cases, no abnormal pleural uptake was seen on the ^{18}F-FDG PET/CT imaging; this might be explained by tumor characteristics. According to the literature, tumors with low metabolic activity such as bronchioloalveolar carcinoma and carcinoid tumors can give rise to false-negative results.[8] In addition, false-negative malign mesothelioma cases were also reported in literature.[9] We observed that ^{18}F-FDG PET/CT imaging was false positive in one patient. False-positive FDG-PET results have been reported in patients with pneumonia, sarcoidosis, pleural fibrosis, round ateletasis, talc pleurodesis, and caseating granulomas. Infectious and inflammatory lesions may have increased ^{18}F-FDG accumulation and mimic tumor. In most cases, these findings are attributed to the increased metabolic state of accumulated inflammatory cells.[10]

Our results show that the ROC curve for SUVmax had the highest accuracy at differentiating malignant mesothelioma from benign lesion. With a SUVmax threshold of 2.2, sensitivity, specificity, positive predictive value, and negative predictive value for detecting malignant mesothelioma were 94.1%, 100%, 100%, and 93.3%, respectively. We show that a SUVmax values greater than 2.2 is always associated with malignancies and require biopsy. On the other hand, we did not detect any benign lesions above SUVmax of 2.2. The high negative predictive value of ^{18}F-FDG PET in our study indicates that lesions with a SUVmax values less than 2.2 are probably benign and usually do not need further invasive diagnostic work-up. However, it should be noted that the predictive values of a test depend on the prevalence of the abnormality in the patients being tested. Therefore, we believe that close follow-up is necessary in most of these patients.

The diagnosis of MPM requires immunohistopathological analysis of tissue samples, which were obtained from pleural lesions by invasive procedures such as CT-guided pleural biopsy, thoracoscopy, or thoracotomy. However, noninvasive diagnostic methods may be important for patients in bad state or patients who do not want any invasive biopsy procedures. It is also possible to identify cases with a low probability of MPM, possibly related with negative predictive value, which could be calculated with ROC analysis. To improve the diagnosis of MPM, a number of serum or pleural fluid markers have been intensively evaluated, but the research for an acceptable marker has so far been insufficient. Recent reports have raised interest on soluble mesothelin-related peptides, megakaryocyte potentiating factor, and osteopontin as possible markers for diagnosing MPM.[11] An important question is that whether these markers may be used to screen individuals having occupational or environmental risk factors.

Accordingly, recent advances have increased the importance of imaging modalities. Our study group previously reported that the CT findings of "rind-like pleural involvement," "mediastinal pleural involvement," "pleural nodularity," and "pleural thickness more than 1 cm" were independent findings for differentiation of malignant pleural diseases from benign pleural disease with the sensitivity/specificity values of 54/95%, 70/83%, 38/96%, and 47/64%, respectively.[12] Magnetic resonance imaging is superior to CT in the assessment of chest wall and diaphragmatic involvement of mesothelioma.[13] As the most recent nuclear medicine imaging modality, PET imaging with ^{18}F-FDG has been widely used in thoracic oncology primarily to distinguish between benign and malignant disorders, including lung cancer.

Several studies have already addressed the potential role of an increased ^{18}F-FDG uptake in identification of pleural malignancy. The sensitivity of ^{18}F-FDG PET/CT in our patient group is similar to previously reported sensitivities. Benard et al.[14] reported that FDG-PET is a sensitive imaging method for differentiating malignant from benign involvement in patients with asbestos exposure who present with pleural effusions or pleural thickening on CT scanning. Also, they concluded that using an SUV of greater than 2.0 to differentiate benign from malignant disease, the sensitivity, specificity, and overall accuracy of the method were 91%, 100%, and 92%, respectively. In a prospective study, Kramer et al.[9] studied 32 patients and concluded that qualitative assessment of pleural thickening with PET accurately discriminates between malignant and benign pleural thickening, with a high accuracy and negative predictive value. They also suggested that patients with pleural thickening and negative PET findings may be followed up using only CT instead of pathologic diagnostic procedures. Similarly, Qureshi and Gleeson[5] reported that patients with pleural thickening and a negative PET scan do not routinely require histologic verification but do require radiologic follow-up. A study by Carretta et al.[15] suggested that ^{18}F-FDG PET may have a great

potential, both in the differential diagnosis of pleural diseases and in the evaluation of the response to treatment.

Possible application of ^{18}F-FDG PET/CT for imaging of mesothelioma are to detect and stage the extent, to differentiate between malignant and benign lesion in patient with asbestos exposure, assessment of disease progression, and evaluation of disease response to treatment.[4] ^{18}F-FDG PET/CT increases the accuracy of overall staging in patients with MPM and significantly improves the selection of patients for curative surgical resection.[16] Specifically, ^{18}F-FDG PET/CT detects more extensive disease involvement than that shown by other imaging modalities and is particularly useful in identifying occult distant metastases.[17] ^{18}F-FDG PET/CT is a noninvasive imaging technique, which has recently been validated for the assessment of therapy response in patients with malignant mesothelioma.[18] ^{18}F-FDG PET/CT also can predict the prognosis of MPM.[19] In our study, we observed that ^{18}F-FDG PET/CT can be useful to decide further investigations for the patients who had asbestos-related pleural diseases.

In our study, our sample size was relatively small. This is the limitation of our study. On the other hand, although ^{18}F-FDG–PET/CT has proven to be the best noninvasive imaging tool for differentiation of malignant disease, it is a relatively expensive imaging technique yet.

In conclusion, the early discrimination of clinically aggressive malignant mesothelioma would be clinically useful. The preliminary findings of this pilot study suggest that adding ^{18}F-FDG PET/CT imaging to the diagnostic workup of patients with malignant mesothelioma may limit the number of unnecessary invasive procedures or may be useful to decide the indication of invasive methods for cases with high suspicious of MPM. Accordingly, ^{18}F-FDG PET/CT should be considered as noninvasive diagnostic test for distinguishing of malignant pleural disease from benign lesion.

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